

Cystic tumor of atrioventricular node: a narrative systematic review

CTAVN review

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Abstract

Aim: Cystic tumor of atrioventricular node (AVN) is a very rare benign cardiac tumor-the silent cause of sudden death. This study aimed to review all studies and summarize literature knowledge of cystic tumor of AVN in addition with recent case reports.

Material and Methods: It was performed a systematic analysis based on MEDLINE/PubMed, WOS, Researchgate, Google scholar databases. 67 studies with a confirmed pathological diagnosis of cystic tumor of AVN were included.140 patients diagnosed with cystic tumors of AVN were listed. 24 patients were diagnosed antemortem. Following exclusion of duplicated patients, 116 postmortem patients were evaluated.

Results: After adding new cases, the mean age was found to be 39.89, and the expected female-to-male ratio was 1.8:1. Dyspnea and palpitation were the most commonly reported symptoms. Third-degree AV block was the most common ECG finding. The tumors were mostly located in the AVN region. In most patients' medical history, previous congenital heart block in various degrees existed; it might be a relation with cystic tumor of AVN and misdiagnosed 'congenital' heart block.

Discussion: It has been advised to take a routine section of the AVN during autopsy in all cases of sudden death. This is the largest review on cystic tumors of AVN in the literature so far.

Keywords

congenital, cardiac tumor, atrioventricular node, arrhythmia, complete heart block

Introduction

Cystic tumor of atrioventricular node (AVN) is a rare primary congenital cardiac tumor and comprises of 2.7% of cardiac tumors and is the most common primary cardiac tumor causing sudden death [1–9]. It was first described in 1911 as a lymphangioendothelioma [10,11].

Various terms have been used, such as angioendothelioma, mesothelioma of the AVN, celothelioma, benign mesothelioma of Mahaim, lymphangioma, endothelioma, inclusion cyst, polycystic tumor, endodermal heterotopia, endodermal rest, dysontogenetic endodermal tumor, a remnant of the truncus arteriosus division, hamartoma, epithelial inclusion, chronic lymphangitis proliferans, adenoma-like tissue malformation of the serosal epithelium, heterotopic epithelial replacement of the AVN, congenital endodermal heterotopia, Tawarian node, and Tawarrioma [11].

Cystic tumor of AVN is known to be benign and has a histologically cystic nature [12]. It is typically located at the base of the right atrium, in a similar area of AVN within the Koch's triangle [1]. Clinical presentations are sudden death, syncope attack, complete heart block or lethal arrhythmia in general [13]. It is sometimes found in an autopsy incidentally [12].

This review aimed to investigate recent clinical studies; clinical presentation, relation with different congenital heart diseases, surgical treatment, medical follow-up, prognosis, and summarize the literature knowledge of cystic tumor of AVN, in addition to recently published case reports in the literature.

Etiology

It is believed that the cystic tumor of AVN originates from congenital rests of endodermal origin [4,9]. A recent study suggested that the origin of this tumor may be solid cell nests of the thyroid tissue [14]. The tumor has been thought to be a dilatation of a cyst instead of a tumor enlargement [15,16].

Presentation

A cystic tumor of AVN is a congenital benign mass. First case report- a postmortem diagnosis- was published by Armstrong and Monckeberg in 1911 [10]. The mean age of diagnosis is 38 years with a range from birth to 96 years, and the majority of patients are female [1,15,17]. Associated diseases are congenital heart diseases such as atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA); hypoplastic left heart syndrome (HLHS); pulmonary hypoplasia; and transposition of great arteries (TGA); thyroglossal duct cysts, cysts in the ovaries and breasts, encephalocele; and Emery-Dreifuss muscular dystrophy [9,18].

The main presentation of cystic tumors of AVN is particularly related to conduction system pathologies [15]. Most common symptoms are palpitation, chest pain, shortness of breath, dizziness, syncope, and sudden cardiac death [9,19]. Other events are heart attack, stroke [9].

The most common arrhythmia is complete atrioventricular (AV) block, which is predominantly relevant to sudden cardiac death [19]. Other rhythm disturbances are 1st or 2nd degree heart blocks, bradycardia, intraatrial conduction defect, paroxysmal atrial arrhythmia, junctional escape rhythm, and spontaneous intermittent preexcitation [1,13,20,21].

Diagnosis and Differential Diagnosis

Regarding literature knowledge, on physical examination, an obvious auscultation evidence of right-sided valves due to an occlusive effect of the cystic tumor of AVN is not encountered. In most cases, patients suffer from different degrees of heart block or palpitation. Frequently, in patients' medical history, a relevant cardiac arrhythmia occurs in early ages or a few years previously before the cystic tumor of AVN has been diagnosed [13]. Electrocardiogram (ECG) and Holter monitoring determine various degrees of arrhythmia. Magnetic resonance imaging (MRI) and computed tomography (CT) provide detailed information about tumor size, anatomical structures in close proximity, and the exact location of the tumor [1]. Coronary angiography is not necessary unless the patient requires additional examination for co-morbid coronary artery disease; however, with the aid of a selective angiogram, a demonstration of a 'tumour flush' or an abnormality of the course of this artery may suggest the existence of an AVN tumour in an alternative way [22].

In differential diagnosis for cardiac cysts, bronchogenic cysts, and mesothelial cysts should be investigated. In addition, teratoma and histiocytoid cardiomyopathy should be suspected for pediatric patients [3,23]. Bronchogenic cyst develops on the epicardial surface and includes mesoderm and endoderm layers [9]. Mesothelial cyst develops on the surface of the heart and includes mesoderm and endoderm layers, and is larger than a cystic tumor of the AVN [9]. Teratoma includes endoderm, mesoderm, and ectoderm [24].

Management

Because of a limited number of cystic tumors of AVN in the literature- most of them were diagnosed postmortem- a standard management or surgical resection and therapeutic concepts have not been established, and it's still controversial [21]. Most authors have advocated surgical resection since the exact diagnosis is made [21,25,26]. Ojha et al. reported a permanent pacemaker implantation to palliate complications of complete AV block and inhibit -clear and imminent danger- sudden death for their 55-year-old patient who didn't accept surgical resection [20]. Guillian et al. suggested close follow-up for elderly asymptomatic patients diagnosed incidentally [27]. Similarly, according to their experience with a 42-year-old asymptomatic patient except a 3rd degree AV block diagnosis, Alrashidi et al. advised close follow-up [28].

Surgical Approach

Two different approaches have been suggested in the literature: 1. A total resection of the tumor [29]. 2. A partial resection in case of patients in poor preoperative condition or a huge tumor [3,5,25]. The majority of surgical treatments were realized by standard median sternotomy under cardiopulmonary bypass (CPB); on the other hand, there are only two patients operated on with a minimally invasive approach without cross-clamping of the aorta [13,26].

Histopathological Characteristics

Tumor size may be in a range of visually unnoticeable size to macroscopic size [1]. This tumor seems to imitate a thickening of the basis of the interatrial septum (IAS), sometimes noticeable only in a routine pathological examination in autopsy,

to understand the exact reason for the patient’s sudden death [6,9]. The exact address of the tumor is similar to AVN, in other words, in Koch’s triangle, which is framed by the ostium of the coronary sinus in the right atrium to the membranous septum, anulus of the tricuspid valve septal leaflet and tendon of Todaro [1]. Only one case has been published in the thyroid gland [30].

Prognosis and Recurrence

Clinical manifestation of cystic tumor of AVN varies. The majority of cases were diagnosed postmortem, and it has been shown that the tumor has a relationship with fatal cardiac dysrhythmia, even with first-degree to complete heart block, and sudden cardiac death is not a surprising result, even though it is accepted as a benign congenital pathology [3,31]. The majority of postmortem pathological investigations showed that the effect of arrhythmia due to the AVN invaded tumor is independent of tumor size, as proven by microscopic-sized tumors found in autopsy series.

Materials and Methods

A keyword search of MEDLINE/PubMed and Web of Science, researchgate, Google scholar was performed to identify the relevant case reports and case series in English using the following terms: angioendothelioma, mesothelioma of the AVN, celothelioma, benign mesothelioma of Mahaim, lymphangioma, endothelioma, inclusion cyst, polycystic tumor, endodermal heterotopia, endodermal rest, dysontogenetic endodermal tumor, a remnant of the truncus arteriosus division, hamartoma, epithelial inclusion, chronic lymphangitis proliferans, adenoma-like tissue malformation of the serosal epithelium, heterotopic epithelial replacement of the AVN, congenital endodermal heterotopia, Tawarian node and Tawarrioma. The PRISM flowchart is shown in Figure 1.

Ethical Approval

This study did not require ethical approval according to the relevant guidelines.

Results

The present study revealed that the expected female-to-male ratio was 1.8:1 and a mean age of 39.89 years. A total of 140 patients were investigated. Twenty-four patients were diagnosed antemortem. Nineteen of them were female, highlighting the female dominance. In general, antemortem diagnosed alive patients had mostly cardiac symptoms such as palpitation, heart block in various degree. Almost all of them were investigated first via ECG and transthoracic echocardiogram. Computed tomography and MRI were the second-choice diagnostic modalities. The most encountered additional congenital cardiac pathology was ASD. Only in one patient, a VSD was detected. Characteristics of tumors in antemortem diagnosed patients and preferred treatments were collected and summarized. The tumor localizations were in the region of Koch’s triangle in general. In some cases, tumors were localized in the basal portion of IAS. Among them, only five patients had a partial resection so as not to trigger a complete heart block [3,25,26,35,37]. Ten patients required new-onset permanent pacemaker implantation. Long-term follow-up data were not found in the literature for all of the cohorts. Only a 5-year

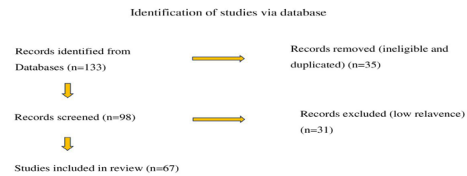


Figure 1. Flow diagram of the study

follow-up period of one patient is available in the literature [4]. Data from patients with postmortem diagnosis in autopsy were collected from the literature. Some of the patients had been documented in different series belonging to various authors. After excluding duplicated patients, 116 postmortem diagnosed patients were evaluated. All postmortem patients were investigated during the autopsy to understand the exact reason for sudden death. Therefore, due to the fact that the previous symptoms of patients were not fully documented in all literature studies, these data weren’t fully found. Additional congenital heart defects were as follows: 1 VSD, PDA; 1 unknown congenital heart anomaly; 1 VSD with mitral insufficiency (MI); 1 HLHS; 1 pulmonary hypoplasia; and 1 TGA with PDA. The detailed data are provided in Supplementary Tables S1, S2, S3.

Discussion

Cystic tumor of AVN is an extremely rare congenital tumor. It typically presents in adulthood at a mean age of 38 years, ranging from newborns to 96 years, with a female-to-male ratio of 3:1 according to previous studies [12,15,53]. In our study, with the additional new cases, the expected female-to-male ratio was found to be 1.8:1, and the mean age was 39.89 years. Even though being a benign neoplasm, it is an evident reason for sudden death, which is always evaluated in autopsy due to its relevant fatal arrhythmias.

Symptoms, Clinical Manifestation, and Arrhythmia

Clinical manifestations of this tumor varie. Many patients are asymptomatic. Other clinical manifestations are dyspnea, dizziness, unconsciousness, or, in a majority of cases, sudden death. In various cases, patients present with bradycardia, various degrees of heart block in their previous medical history, sometimes since their childhood. When postmortem cases are evaluated, majority have a previous diagnosis of heart block, congenital heart block or permanent pacemaker implantation history. However, some postmortem case reports were about only pathological reports. Therefore, their previous clinical manifestation were not reported. In conclusion, it is difficult to estimate the exact ratio of anticipant arrhythmia. Most cases introduce a previous permanent pacemaker implantation due to the early onset bradycardia or various degrees of heart block. Before the invention of the pacemaker device, these patients were treated with conservative medical treatment for any reason of heart block. Since permanent pacemaker implantation has become possible, symptomatic improvement has become possible. On the other hand, a permanent pacemaker doesn’t prevent patients’ fateful death. In some cases of sudden death, permanent pacemakers were still

working appropriately at the time of postmortem diagnosis at autopsy [59,62]. This dilemma should be investigated in detail. How important AVN cells or HIS are for a permanent pacemaker to properly stimulate the heart remains unanswered. This answer could also contribute to future pacemaker technology.

Diagnostic Methods

All antemortem diagnosed patients had ECG and transthoracic echocardiogram first due to palpitation symptoms. In addition, for further investigation, transesophageal echocardiogram (TEE), CT, and MRI were preferred imaging tests [26]. Only one patient had a coronary angiography test to eliminate coronary artery disease [34]. In addition, Bharati et al. have suggested using coronary angiography, which might determine the supplying artery of the AVN for a suggestive clue about the probable existence of a cystic tumor of AVN [22].

In most cases, echocardiography alone is insufficient for establishing the diagnosis because of the small size of the tumor [29]. To date, only one single case has been described in the literature in which a successful tumor biopsy was performed using stereotactic guidewires under TEE guidance by Alrashidi et al [28]. Alrashidi et al. used a three-dimensional (3D) TEE to determine an appropriate condition for taking a biopsy. During the patient's follow-up over 18 months, they also used serial 3D echocardiography [28].

Size of Cystic Tumor of AVN

Symptoms were not related to the size of the cystic tumor of AVN. Particularly in postmortem pathological examinations for suddenly dead patients, most of the tumors were of microscopic size. The largest tumors were reported by Anderson (8 cm in diameter) in a postmortem investigation and Leiballi (7 cm in diameter) in a living patient [1,40].

Histopathological Characteristics

Although this tumor was previously named mesothelioma of the AVN, primarily based on ultrastructural studies showing its derivation from mesothelial lineage, the exact embryogenesis is still controversial [6]. Cameselle-Teijeiro et al. studied 10 solid cell nests of the thyroid and a case of cystic tumor of AVN of the heart. They remarked similar cellular features which were proving the hypothesis about the cystic tumor of AVN of the heart and the solid cell nest of the thyroid are identical structures. To the best of our knowledge, cystic tumor of AVN, originates from ultimobranchial tissue- which is originated from foregut per se- that constitutes cardiac neural crest cells in cardiac development [14].

Cyst which is a remnant structure from embryological period, is described for producing a yellowish cystic fluid in literature [26]. The more fluid increases the more cyst volume becomes obvious and easy to be diagnosed.

Differential Diagnosis

The differential diagnosis of the cystic tumor of AVN includes several neoplastic and non-neoplastic entities that may involve the central fibrous body or conduction system region. These primarily comprise papillary fibroelastoma, cardiac myxoma with atypical septal attachment, rhabdomyoma, fibroma, and inflammatory or degenerative cystic lesions such as blood cysts, congenital inclusion cysts, and bronchogenic cysts. In addition, non-neoplastic causes of AV conduction disturbance, including sarcoidosis, amyloidosis, and post-inflammatory

or postsurgical fibrosis, may mimic the clinical presentation; however, they typically lack a discrete cystic mass on imaging [35].

Regarding malignant pathologies, metastatic tumors, particularly from lung or breast carcinoma, and primary malignant cardiac tumors such as sarcoma, malignant fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, fibrosarcoma, primary cardiac lymphoma, although exceedingly rare in this location, should be considered in the differential diagnosis. However, all these diseases and malignant tumors can be excluded easily from the cystic tumor of AVN, with a careful correlation of echocardiographic, cardiac MRI, cardiac CT, and histopathological findings is essential to distinguish a cystic tumor of AVN, given its unique predilection for causing complete heart block and sudden cardiac death. The cystic tumor of AVN is generally very small in size and is found to be in a very specific region in the lower part of the IAS or in the region of Koch's triangle.

First of all, among these pathologies, metastatic carcinoma should be excluded. To ensure, the surgeon's opinion about the intraoperative view of the mass and the patient's history of previous cancer should be considered. Conversely, tumors that appear benign and do not contain atypia or mitotic figures may indicate that they are not metastatic carcinoma. Bronchogenic cysts that have larger and single cysts with a muscular wall usually occur on the epicardial surface far from Koch's triangle. Myxoma, the most encountered cardiac tumor, is generally located in the endocardium of the atrial septum near the fossa ovalis. The cells may be arranged in cords or in vasoformative ring structures and cytokeratin stain negative [35].

Female Dominance and Eustrogene

Regarding previous studies concluding the cystic tumor of AVN is encountered with a dominant female patient frequency, such as a female-to-male ratio of 3:1, Ichimata et al. investigated sex hormone receptors on tumor cells [12,15,53,66]. Their study exhibited that tumor cells had prostate-like histological architectures and prostate-like immunohistochemical features. In their investigation, some tumors had glandular epithelium of a subset of cystic tumors of AVN. In a female patient's tumor, androgen receptor and estrogen receptor were negative; progesterone receptor was focally positive in both the inner and outer cells. In their second and third male patients, the androgen receptor showed intermediate positivity in the inner cells; the estrogen receptor and progesterone receptor were positive in the outer cells. Positive expression of both prostate-specific antigen and prostate-specific acid phosphatase were found in the inner cells of both male patients. Ichimata et al. concluded that cystic tumors of AVN may originate from ectopic hindgut-related tissue, which is derived from the primitive endoderm urogenital sinus, similar to the foregut [66]. In the literature, there is no clear evidence of a relation between female dominance and estrogen receptor positivity in cystic tumors of AVN. Differently, in the current study, the female-to-male ratio was found to be 1.8:1.

Follow Up in Regard to Complete or Partial Excision

Treatment options for cystic tumors of AVN are controversial due to their rarity, and there is no clear consensus or established guideline. Sudden death risk, although a permanent pacemaker

or implantable cardioverter-defibrillator (ICD), still remains [26]. A few investigators have published their works in which they used partial resection for the removal of tumors [3,25,26]. For instance, Cheng et al. reported that although the patient underwent partial resection, they required a permanent pacemaker [26]. There is no long-term follow-up regarding tumor recurrence [26].

Fukui et al. reported their experience with partial resection to avoid complete heart block for their patient who had been diagnosed with first-degree heart block at the time of preoperative investigation [25]. Their patient didn't require a permanent pacemaker implantation. After a one year of follow-up via strict echocardiography investigation every two months, no recurrence was observed [25].

Paniagua et al. used partial resection of the tumor to avoid the complete heart block [3]. However, the patient developed atrial flutter, various degrees of heart block with a slow ventricular rate; therefore, the patient required a permanent pacemaker finally [3]. However, a long-term follow-up report is required.

Li et al. reported their experience with partial resection of a cystic tumor of AVN [35]. The patient's long-term follow-up wasn't mentioned.

Stopyra-Początek used partial resection in a patient who had previously received a permanent pacemaker [37]. In the same operation, mitral valve repair was performed due to a mitral valve prolapse. Six months later, the patient was monitored via echocardiography, and no recurrence was found. Unfortunately, long-term follow-up data were not reported.

Follow Up Regarding Surgical Technique: Standard Sternotomy or Minimally Invasive Technique

As mentioned above, there is no clear consensus about the surgical treatment of cystic tumors of AVN. A few case studies provide experiences about minimally invasive surgical techniques. In general, conventional sternotomy and bicaval venous cannulation are still preferred.

The first case under minimally invasive operation circumstances was published by Careddu et al. [13]. Under minimally invasive surgery conditions, without cross-clamping the aorta, the cystic tumor of AVN was excised completely. Following the surgery, a first-degree heart block was observed. On the postoperative 2nd day, a transient complete heart block was observed for a limited time, and nodal rhythm was sustained. Due to the relatively good condition, no pacemaker implantation was made, and after cardiac rhythm was restored spontaneously. However, a persistent complete heart block occurred then, and compulsory permanent pacemaker implantation was performed [13]. The long-term follow-up data is required.

Cheng et al. reported a minimally invasive technique in the surgery of cystic tumors of AVN in moderate hypothermia by using Del Nido cardioplegia [26]. A multi-septated mass was excised, and the remaining edges of the cyst were marsupialized, finally [26]. The patient was discharged in good condition without a permanent pacemaker. Unfortunately, the long-term follow-up data is required.

Limitations

There are several limitations in the current review. First, the data sources primarily relied on retrospective observational studies on the web. Certain parameters, such as patients' age,

pre-diagnostic symptoms, histopathology, tumor invasiveness, and the extent of resection, postoperative long-term follow-up data could not be obtained from each included study as they were not reported. Therefore, an exact statistical comparison couldn't be provided in the current review.

Conclusion

In most patients' medical history, previous congenital heart block in various degrees exists, which might be related to AVN tumor and misdiagnosed as early onset 'congenital' heart block. Therefore, it should be kept in mind that this probability exists in heart blocks of childhood. In addition, for bradycardic patients -such as professional athletes- further imaging tests should be made or more specific imaging methods should be developed, whether the patient is asymptomatic about cystic tumor of AVN [21]. For instance, special intracardiac ultrasound to detect the cystic tumor of AVN in case of unknown cause early onset arrhythmia might be a desired method for diagnosis in the future.

It has been advised to take a routine section of the AVN during autopsy in all cases of sudden death, because the cystic tumor of AVN is still one of the most common and silent causes of sudden death [1].

Even though this tumor is a benign congenital tumor, a close co-existence with a congenital heart defect was not observed in the literature.

For diagnostic methods, echocardiography, CT, and MRI should be performed with a focus on the AVN.

To monitor in mid-term follow-up, it is recommended a strict regular echocardiogram every 6 months for the first postoperative year and annually for 3 years.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content, including study design, data collection, analysis and interpretation, writing, and some of the main line, or all of the preparation and scientific review of the contents, and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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